Reply to: "Usefulness of Lead-In phase in determining risk/benefit of telaprevir treatment in patients with HCV cirrhosis"

To the Editor:

We are grateful to Drs. Bruno and Mangia for their interest in our work [1], and we agree that data on response rates by the degree of fibrosis would be useful and would help guide physicians and patients in reaching a decision regarding the value of therapy, following a 'lead-in' phase. However, in a retrospective analysis of study subpopulations in a trial that was not designed, or powered, to answer the question of interest, there is a difficult line to be drawn between an 'appropriate analysis' and 'data dredging'. The REALIZE study [2] was powered to investigate the value of telaprevir in patients who had failed to respond to pegylated interferon and ribavirin and was designed to include a study arm examining the value of a 'lead in' with pegylated interferon and ribavirin. Only half of the enrolled patients therefore received a 'lead-in' reducing the number of subjects whose response to pegylated interferon and ribavirin could be assessed. We believe that a retrospective analysis of patients divided by prior treatment response and response during 'lead-in' is appropriate, but to sub-divide the population further is, in our view, an analysis too far. The number of null-responder patients with cirrhosis who responded during the lead in phase was 7 – in our view to quote response rates following telaprevir based on such a small number of patients is of limited value and is potentially harmful – clinicians and patients should not be encouraged to base their treatment decisions on subset analyses with very wide confidence intervals, as such decisions are likely to be incorrect. We recognize that studies with other drugs where all patients receive a lead-in may recruit sufficient patients for a meaningful analysis, but for telaprevir where the 'lead in' is optional and for the REALIZE study, where only half of the patients received a 'lead in', we believe that further sub-analyses are not appropriate. We accept that others would take a different approach to the data and we accept that the desire for data sometimes overrides the desire for informative data. However, we do not believe that publication of results from very small subsets of patients should be encouraged.

Conflict of interest

Consultancy work and advisary boards for Janssen, Roche, Merck, Gilead, Novartis, BI and BMS.

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Response assessment methodologies in hepatocellular carcinoma: Complexities in the era of local and systemic treatments

To the Editor:

Although the mainstay of hepatocellular carcinoma (HCC) treatment has been locoregional, new systemic agents have demonstrated significant improvement in time-to-progression (TTP) and survival, leading some to postulate TTP as a surrogate of survival. While there is some rationale supporting this concept in advanced disease, complexities in HCC imaging should temper expanding this enthusiasm to early/intermediate disease until more robust evidence is available. Several examples of this lack of correlation exist in the radiofrequency ablation (RFA), chemoembolization (TACE)/radioembolization, and systemic therapy literature. Although we agree with EASL-EORTC guidelines that mRECIST helps move the field forward, several imaging complexities remain unaddressed [1,2]. These were highlighted by our core imaging research group following a formal review of 463 HCC patients (1818 scans) treated with chemoembolization/radioembolization [3,4].

The first imaging complexity relates to arterial embolic therapies. Since these are performed at staged intervals, imaging follow-up involves the simultaneous radiologic interpretation of treated/untreated disease. This creates difficulty in assessing response; should response only be measured in the treated lesion(s)? How should untreated targets be considered if they have sufficiently enlarged to meet progressive disease criteria? Should imaging only be assessed when all tumors have been treated and if so, how should patients never completing all treatments (toxicities/decompensation) be reported? [5,6]. These methodological nuances are under-reported in locoregional therapy studies. Accurately assessing response/progression (or lack thereof) in the liver is critical since HCC progression is predominantly local [7]. This is also of importance since it suggests that the clinical sequelae of progression may be dependent on the treatment received (see Clinical scenarios, Supplementary information). These concepts further suggest that new (automated)

tools should focus on response and progression in the liver (as opposed to extrahepatic sites).

The second issue relates to "confirmatory progression". Evaluating cirrhotic livers for new lesions can be quite challenging. Hypervascularity/washout is not a perfect criterion. It is not uncommon for equivocal lesions to become suspicious of HCC, yet at follow-up, become less conspicuous. Hence, confirmatory progression (particularly of new nodules) in HCC should be considered. This approach will minimize premature discontinuation of treatment. We have observed this artifact where a "new nodule" in a patient on sorafenib is declared as progressive disease (PD) with treatment discontinuation. At follow-up, despite no treatment, the lesion has disappeared, suggesting sorafenib was prematurely discontinued (PD overcall).

The third issue relates to retrospective adjudication. Guidelines suggest that an equivocal lesion, ultimately determined to represent an HCC, should be retrospectively adjudicated to the time it was first observed. It is therefore possible to exhibit a TTP of 0 if a baseline equivocal lesion was only later confirmed to be HCC. Although unlikely, we have observed this phenomenon in varying magnitudes. In this scenario, retrospective adjudication weakens any TTP/survival correlation.

The fourth issue relates to the need to capture HCC-related portal vein thrombosis in response guidelines. Despite no change in index lesion size, HCC treatment may result in the retraction/disappearance of portal vein thrombosis (PVT). We acknowledge that mRECIST appropriately labels PVT as non-target with subjective response/progression assessment. Imaging tools that objectively/consistently quantify this relevant finding are needed.

The fifth point involves the interobserver reproducibility of measuring the longest uni/bidimensional diameter of enhancing tissue. While RFA may result in clear zones of necrosis and viable tissue, this is not the case with embolotherapies. We have encountered challenges when multiple readers attempted to reliably define the same (or comparable) areas of enhancing tissue following embolotherapy. This is a critical issue needing further investigation, with solutions that may potentially require automated imaging tools.

Finally, and potentially most importantly, the mechanism of action and the time-dependence of response are often ignored. Embolic therapies lead to reduced tumor enhancement because of vascular occlusion. Since this finding may be observed on a contrast scan immediately after embolization, this cannot simply be labeled as necrosis. Alternatively, non-embolic therapies (Yttrium-90/radiotherapy/systemic) require time for response to manifest and in fact, may not lead to pronounced "necrotic" features. The lack of reduction in enhancement does not necessarily suggest treatment failure. Rather, it may represent tissue in the process of undergoing cell death, with lack of enhancement observed at a later date. Furthermore, although systemic agents may lead to reduced enhancement, this finding of "necrosis" may not necessarily represent cell death. In fact, tumoral enhancement may quickly return once the systemic agent is discontinued, suggesting hypoenhancement may not necessarily represent "necrosis" as we understand it pathologically [8,9].

We believe enhancement criteria are skewed towards therapies that mechanistically cause avascularity (RFA, TACE), ignoring those not dependent on arterial occlusion (Y90/radiotherapy/systemic). The enthusiasm for new imaging methodologies should be tempered until more controlled studies are completed, including radiology–pathology correlation; there is only one such study to date [10]. The above mentioned methodological complexities/nuances, among others, need to be incorporated in future versions of guidelines as we believe this granularity of detail is essential when reporting response in HCC studies.

When it comes to HCC and response assessment, there is still a lot of work to do including standardization, interobserver reproducibility, volume analysis, radiology–pathology correlation and imaging surrogates of survival. While automated software appears to be an attractive tool for response assessment, further research and validation are needed before being able to implement these in routine clinical care.

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Conflict of interest

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.01.021.

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Efficacy of interferon-based antiviral therapy on the risk of hepatocellular carcinoma of patients with chronic hepatitis C: Further evidence in decompensation cirrhosis

To the Editor:

We read with great interest the paper by Eiichi Ogawa and colleagues [1], accepted for publication in the *Journal of Hepatology*. The authors performed a large-scale, multicenter, prospective study and presented important data regarding the observation that sustained virological response (SVR) and transient virological response (TVR: defined as relapse or breakthrough) were associated with a lower risk of development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C, with or without cirrhosis, when compared with non-virological response (NVR). However, cirrhotic patients with advanced disease, namely decompensated cirrhosis, have been excluded from their study. No study to date has provided evidence that virus suppression and elimination after interferon (IFN)-based antiviral therapy reduce the risk of HCC in this difficult-to-treat population. We performed a prospective pilot trial to investigate the safety and efficacy of pegylated/standard IFN-α combined with ribavirin for decompensated cirrhosis patients with HCV infection.

From January 2008 to January 2011, 50 consecutive, IFN-naïve HCV decompensated cirrhotic patients were treated with PegIFN-α-2b at 1.0–1.5 μg/kg/week or standard IFN-α-2b, 3MU, thrice weekly, plus ribavirin at 800–1000 mg/day for 48 weeks, with a low accelerating dosage regimen. The diagnosis of decompensated liver cirrhosis was made when a patient had experienced one or more of the following clinical symptoms: ascites, variceal bleeding, spontaneous bacterial peritonitis (SBP), and encephalopathy, which referred to Iacobellis' and our previous studies [2,3]. Patients with HCC, chronic renal failure, unstable cardiovascular disease, severe chronic obstructive lung disease, co-infection with immunodeficiency or hepatitis B viruses, current alcohol abuse, platelets <35,000/μl, neutrophils <1000/μl, haemoglobin <100 g/L, or Child-Pugh class C were excluded [2,3]. Patients were routinely monitored for SVR, TVR, and NVR according to the accepted guidelines and Ogawa's study [1,4]. The primary end point of our study was the assessment of HCC development after treatment; the length of the follow-up period was calculated from the end of the antiviral therapy to the diagnosis of HCC or the last follow-up visit. The secondary end point was to investigate further events of decompensation after treatment.

The baseline characteristics and clinical prognosis of the 50 studied patients as classified by treatment outcome, are shown in Table 1. There was no HCC development during antiviral treatment. Of all patients, 9 (18%) required premature treatment withdrawal because of adverse effects and/or poor virological response. Of the studied patients, 21 achieved SVR (42.0%), 15 were TVR (30.0%), and 14 (28.0%) were NVR. Median follow-up off-therapy was 29 (range 8–45) months, seven (14%) patients developed HCC, including 2/21 with SVRs (9.5%), 1/15 with TVRs (6.7%) and 4 of 14 with NVRs (28.6%), respectively. During the follow-up period, 4/21 patients with SVRs (19.0%), 5/15 (33.3%) with TVRs and 13 out of 14 without virological response (92.9%) experienced further events of decompensation (p <0.001).

In patients with HCV compensated cirrhosis, a significant reduction in the annual incidence of HCC has been reported after SVR [5,6]; and Ogawa and colleagues found that compensation cirrhotic patients with TVR also have a lower incidence rate of HCC compared with patients with NVR. For decompensation cirrhotic patients in our study, although a low number of patients developed HCC and the observation period was short, the Kaplan–Meier curves for the end point of HCC showed a noticeable separation of both patients with SVR and TVR from those with NVR, at approximately 16 months of post-treatment follow-up (overall: p = 0.048, SVR *vs.* TVR: p = 0.887, SVR *vs.* NVR: p = 0.045, and TVR *vs.* NVR: p = 0.089 by Log-rank test) (Supplementary Fig. 1). It is inconsistent with the results of the study showing that HCC developed at comparable rates in decompensation cirrhotic patients with and without SVR during a 5-year follow-up, upon completion of the combination therapy [7]. One possible explanation for the discrepant results may be that the efficacy of TVR on the risk of HCC was included in no SVR group, in their study [7]. An intriguing finding from our study is that 72% (36/50) of decompensation cirrhotic patients, compared with 68% (102/150) of compensation cirrhotic patients in Ogawa and colleagues' study, had an undetectable HCV RNA at the end of treatment. Asians have a significantly higher